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GetReal: from efficacy in clinical trials to relative effectiveness in the real world

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Abstract

The GetReal consortium ("incorporating real-life data into drug development") addresses the efficacy–effectiveness gap that opens between the data from well-controlled randomized trials in selected patient groups submitted to regulators and the real-world evidence on effectiveness and safety of drugs required by decision makers. Workpackage 4 of GetReal develops evidence synthesis and modelling approaches to generate the real-world evidence. In this commentary, we discuss how questions change when moving from the well-controlled randomized trial setting to real-life medical practice, the evidence required to answer these questions, the populations to which estimates will be applicable to and the methods and data sources used to produce these estimates. We then introduce the methodological reviews written by GetReal authors and published in Research Synthesis Methods on network meta-analysis, individual patient data meta-analysis and mathematical modelling to predict drug effectiveness. The critical reviews of key methods are a good starting point for the ambitious programme of work GetReal has embarked on. The different strands of work under way in GetReal have great potential to contribute to making clinical trials research as relevant as it can be to patients, caregivers and policy makers.

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The randomized clinical trial is the most reliable study design to determine the efficacy and safety of drugs. However, the clinical trials system has been described as “broken,” “in crisis” and “not fit for purpose”: many trials do not achieve patient enrolment targets; spiralling costs and complex regulatory and monitoring requirements prevent the conduct of others; and many completed trials do not answer clinically relevant questions or are not applicable to everyday medical practice but are driven by commercial considerations (DeVita, 2008; Vickers, 2014; Loudon et al., 2013). As a consequence, fewer trials that are relevant to patients, caregivers and policy makers are carried out, and the evidence on the benefits and risks of drugs is becoming less reliable.

Several initiatives have been established in recent years to remedy this situation. In the USA, Duke University and the Food and Drug Administration established CTTI, the Clinical Trials Transformation Initiative (Tenaerts et al., 2014). CTTI’s mission is “to promote practices that will increase the quality and efficiency of linical trials, ”with the aim to create a clinical trials system that is “patient centered and efficient, enabling reliable and timely access to evidence-based prevention and treatment options.” The initiative has generated evidence and formulated recommendations, for example, to streamline risk-based trial monitoring and the ethical review process. Similarly, Oxford University in the UK, McMaster University in Canada and Duke have joined forces to form the Sensible Guidelines Group to “rid clinical trials of undue bureaucracy, maximize patient safety, and improve the efficiency of reaching valid conclusions from large multi-centre randomized studies” (Shurlock, 2013).

Launched in October 2013, “GetReal: Incorporating real-life data into drug development” of the European Union’s Innovative Medicines Initiative is another important development to enhance the efficiency of randomized trials and the quantification of effectiveness and safety of drugs in real-world medical practice. GetReal is a public–private consortium consisting of academia, pharmaceutical companies, health technology assessment agencies, regulators and patient organizations (GetReal consortium, 2016). GetReal addresses the “efficacy–effectiveness gap” (Eichler et al., 2011) that opens between the data from well-controlled randomized studies in selected patient groups submitted to regulators and the real-world evidence (RWE) on effectiveness and safety of drugs, required by decision makers. Decisions on whether a new drug should be made available in a national health system or reimbursed by social insurance requires evidence on its relative effectiveness and safety compared with established treatments and the wider implications including costs of introducing a new therapy. Ideally, such evidence should be made available to regulatory and health technology assessment agencies before the drug enters the market.

GetReal aims to develop methods and tools that support the generation of RWE on the relative effectiveness of new drugs that could inform decision-making before the drug is launched. The GetReal consortium works with stakeholders to (i) develop a framework for the acceptability of RWE for estimating the effectiveness of new medicines (workpackage 1), (ii) study the scientific validity of RWE, including non-randomized study designs, and analytical approaches and drivers of effectiveness (workpackage 2), (iii) examine the challenges and possible solutions to performing pragmatic trials earlier in the development process, in particular prelaunch or peri-launch (workpackage 3), (iv) develop evidence synthesis and modelling approaches to generate RWE, based on combination of both randomized and observational study data (workpackage 4) Workpackage 4 will be of particular interest to the readership of Research Synthesis Methods.

In workpackage 4, we examine how estimates of the relative efficacy of drugs in clinical trial populations, their relative effectiveness in real world populations and their relative effectiveness in the real world of a healthcare systems can best be obtained, using data from phase II/III clinical trials and from real-world clinical databases and registries. Table 1 summarizes the questions asked,

moving from the randomized clinical trial setting to real-life medical practice, the evidence required to answer these questions, the populations to which estimates will be applicable to and the methods and data sources used to produce these estimates.

We use case studies of the treatment of chronic diseases, for example, schizophrenia, depression and rheumatoid arthritis, to examine different methodological approaches for combining both randomized and observational study data, both using aggregate study data and using individual participant data. For example, we use network meta-analysis approaches of aggregate study results to obtain estimates of relative efficacy from several randomized trials. One of the drugs in the network is, for the sake of the argument, designated as the "new kid on the block," and the trials of this drug are assumed to be prelaunch, whereas the other drugs are assumed to be on the market. Subsequently, individual participant data (IPD) provided by the participating pharmaceutical companies and observational data from clinical databases and disease registries are combined to identify important factors that modify the drug's relative effectiveness and to estimate its performance in patient populations that will likely receive the drug after launch. Of note, at this stage, the relative effectiveness of the drug continues to be estimated under randomized study conditions, rather than real-world conditions (Table 1).

For example, adherence to treatments is implicitly assumed to correspond to that observed in the phase II/III trials. The next step is to account for the messy real world, where doctors decide who will receive the new drug, influenced by guidelines, patient characteristics and preferences, and other factors. In order to gauge relative effectiveness, these decisions need to be understood as well as the possible confounding factors that may be associated with the probability both of receiving the drug and of developing the outcome and the variables that may be associated with the treatment (but not with the outcomes) or of variables associated with outcomes (but not treatment). The likely adherence to the new drug and to the comparator drugs is also relevant. Empirical evidence on these factors will typically be scarce, or absent. Drawing directed acyclic graphs and in-depth discussions with clinicians are helpful to understand how the different variables are likely to interact and what predictive model might be most appropriate (Westreich and Edwards, 2015).

It is good practice first to critically review the methods and applications that will be important in a research programme, to gain an understanding of the relevant strengths and limitations. In this issue and a previous issue of the journal, GetReal investigators present reviews of common methods used for network meta-analysis (Efthimiou et al., 2016), IPD meta-analysis (Debray et al., 2015) and mathematical modelling to predict drug effectiveness (Panayidou et al., 2016). In their review of network meta-analysis methods, Efthimiou et al. summarize the key issues involved, including novel methods for measuring and detecting inconsistency in the network, dealing with effect modification, ways for adjusting for possible sources of bias and the reporting of the results of a network meta-analysis (Efthimiou et al., 2016). IPD meta-analysis is widely considered to be the gold standard in meta-analytic research, but in their review, Debray et al. stress that they are no panacea to the limitations of the included studies. Also, IPD meta-analyses are major undertakings, which cannot be performed ad hoc or on a shoe string, and their potential advantages, for example, the powerful investigation of interaction and subgroup effects, must be carefully weighed against the extra efforts involved (Debray et al., 2015). Finally, Panayidou and colleagues comprehensively searched for studies that predicted real-world effectiveness from randomized controlled trial data. Of note, they found only 12 articles and four modelling approaches, mainly Markov multistate models (Panayidou et al., 2016). Although most studies included sensitivity analyses, external validation was rarely performed.

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The critical reviews of the key methodologies published in the Research Synthesis Methods are a good starting point for the ambitious programme of work the GetReal consortium has embarked on. The different strands of work under way in GetReal have great potential to contribute to making clinical trials research as relevant as it can possibly be to patients, caregivers and policy makers.

Table 1. From efficacy to relative effectiveness in the real world.

Steps and questions	Outcomes of interest	Applicability to patient populations	Data sources	Methodology	Conditions
1) How efficacious and safe is this drug?	Efficacy, safety	Typical patients included in clinical trials	Phase II/III randomised clinical trials	Clinical trials, standard meta-analysis	Study conditions
2) How efficacious and safe is this drug compared with alternative therapies?	Relative efficacy, relative safety	Typical patients included in clinical trials	Phase II/III randomised clinical trials	Network meta-analysis	Study conditions
3) How effective and safe is this drug compared with alternative therapies, in patients who will likely receive it post-launch?	Relative effectiveness, relative safety in predicted study populations	Patients predicted to receive the drug post-launch	Phase II/III randomised clinical trials, clinical databases and registries	Individual patient data network meta-analysis and meta-regression	Study conditions
4) How effective and safe is this drug compared with alternative therapies, in the patients who will likely receive it in the real world of a healthcare system?	Relative effectiveness, relative safety in predicted real-world populations	Patients predicted to receive the drug post-launch in a given healthcare system	Phase II/III randomised clinical trials, clinical databases and registries, expert opinion, patient preferences	Mathematical modelling	Real-world conditions

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